Pharmacology for Nursing Care

Prepared

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Chapter 1: Introduction

- **Four Basic Terms—**
  - **Drug: any chemical that can affect living processes**
  - **Pharmacology: the study of drugs and their interactions with living systems**
    - **Chemical properties**
    - **Biochemical and physiological effects**
    - **Absorption, distribution, metabolism and excretion**
  - **Clinical Pharmacology: study of drugs in humans**
  - **Therapeutics: use of drugs to diagnose, prevent and treat illness**

Definitions:

- **Define Living--**
  - **Respiration- energy formation**
  - **Metabolism- anabolism and catabolism**
  - **Reproduction- DNA replication and cell division**
- **Cell types--**
  - **Eucaryotic cells:**
    - **Contain ribosomes (80S), nucleus, mitochondria, ER, Golgi**
  - **Procaryotic**
    - **Contain ribosomes (70S), NO (mitochondria, nucleus, ER, Golgi)**
- **Viruses—**
  - **Contain NA (DNA or RNA not both), capsid, and no other organelles**

Definition of Disease

- **Disease occurs when:**
  - **Enough cells become dysfunctional**
  - **Enough cells die and organ loses function**
- **Diseases can be due to:**
  - **Autoimmune**
  - **Procaryotic: bacteria (cause disease 1º by toxin release, not by direct invasion into cells and killing of cells))**
  - **Viruses: cause disease 1º by lysis of infected cells**
  - **Chemicals- environment, pollution**
  - **Drugs- medicinal or otherwise**

Properties of Ideal Drug

- **Effectiveness:**
  - **A drug that elicits the response it was meant to (FDA approved with appropriate experiments)**
- **Safety:**
  - **Safe even at high concentrations and for long periods of administration (no such thing)**
    - **Reduced by proper administration (iv, ip, im, sc, etc…)**
    - **No habit forming aspects**
    - **No side effects (resp. failure, immune reaction, etc…)**
- **Selectivity:**
  - **Selective for specific reaction with no side effects**
    - **Cramps, fever, nausea, depression, anemia, etc…**

Additional Properties of Ideal Drug (*no drug is ideal!*)

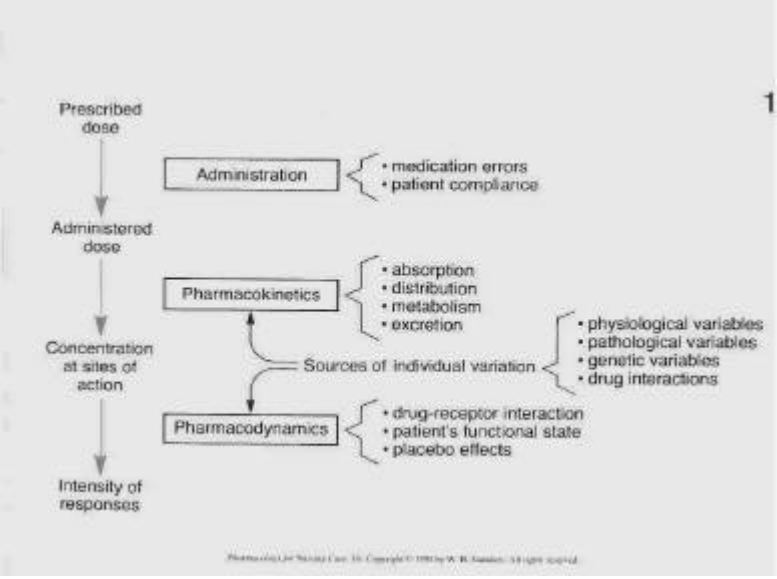
- **Reversible action-** ***removal w/i specific time (1/2 life is short but potent during that time)***
- **Predictability-** ***know how patient will respond***
- **Ease of Administration-** ***number of doses low and easy to administer (inc. compliance & decrease errors)***
- **Freedom from drug interactions-** ***should not augment or decrease action of other drugs or have adverse combined effects***
- **Low Cost-** ***easy to afford (especially with chronic illness)***
- **Chemical Stability-** ***no lose of effectiveness with storage***
- **Possession of a simple generic name-** ***easy to remember and pronounce***

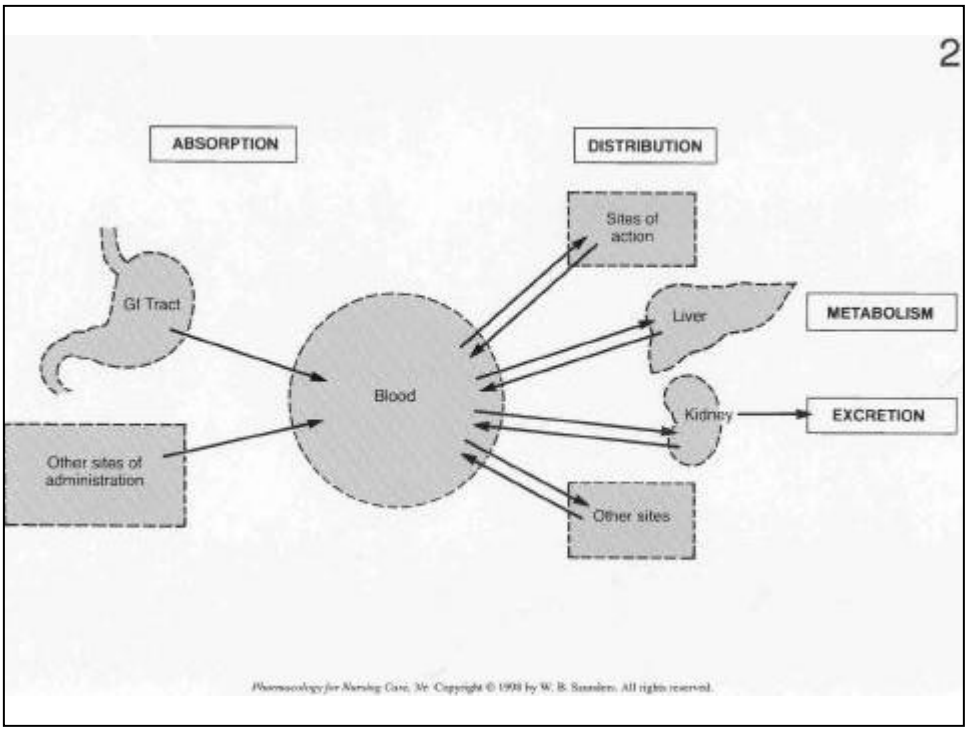
Therapeutic Objective

To provide maximum benefit with minimum harm

Factors that determine Intensity of Response

- **Administration- dosage size and route** ***(because of errors in administration routes and dosage and at wrong time there are many discrepancies in what patient gets and could cause more harm than good)***
- **Pharmacokinetic processes-**
  - ***1) drug absorption***
  - ***2) drug distribution***
  - ***3) drug metabolism***
  - ***4) drug excretion***





- **Pharmacodynamics-**
  - **Once a drug has reached is site of action, pharmacodynamic processes determine the type of response and intensity**
    - **Drug must first bind to its specific target site at (*RECEPTOR*) that may be a chemical, a protein on a cell or in blood or tissue spaces, or on a bacteria or virus (i.e., heparin, antibody, leukotriene receptor (new), penicillin, etc…)**
    - **Followed by a sequence of events that result in response (inhibition of clotting, inhibition of peptidoglycan synthesis, inhibition of inflammation, blocking of virus, etc…). Tolerance to morphine will cause less of a response & placebo effects may help determine response**

- **Sources of individual variation**:
  - **Each patient is unique in ability to respond and to how they each respond, but formation of "IDEAL DRUG" will lessen this variation**
    - **Age- very important factor**
    - **Sex- due to hormonal differences**
    - **Weight- less effective and longer lasting in obese individuals (storage in fat)**
    - **Kidney & liver functions - elimination of drug**
    - **Genetic variables- tolerance, allergy (though not always genetic)**

Chapter 2: Application of Pharmacology in Nursing Practice

- **Nurse's "*Five Rights of Drug Administration*"**
  - **Use the RIGHT drug**
  - **Give to the RIGHT patient**
  - **Give the RIGHT dose**
  - **Give by the RIGHT route**
  - **Give at the RIGHT time**
- **Must also be ready to respond to interaction between drug and patient (i.e., must be aware of drug REACTIONS and SIDE EFFECTS)**

Nurse must have knowledge of…

- **Patient history and drug usage**
- **What medications are appropriate and be aware of drug interactions (cooperation between doctor, pharmacist and nurse a must)**
- **Drug actions and look for abnormal effects**
- **How to be a patient advocate- check for mistakes on part of doctor or pharmacist!!**
  - **Do NOT blindly follow Dr's orders-- THINK and respond to errors [do not be intimidated]**

Patient Care

- **Pre-administration Assessment**
  - **Collecting baseline data to evaluate therapeutic and adverse responses (e.g., get blood pressure data and cell counts to use to determine whether drugs are effective)**
  - **Identifying high-risk patients (e.g., liver/kidney dysfunction, genetic factors, allergies, pregnancy, old age and extreme youth)**
  - **Assessing the patient's capacity for self-care (can they follow directions on their own)**
- **First two assessments are drug specific & last assessment is for any patient and drug**

Drug and Dosage Administration

- **Drugs may have more than one indication, i.e. each may have more than one action depending upon dosage**
  - **Aspirin given in low doses to relieve pain & high doses to suppress inflammation (arthritis)**
- **Drugs can be administered by different routes and dosage depends on route given**
  - **Oral doses usually larger than injected doses (sc, im, ip, im, iv) and may be fatal if given by incorrect route**
- **Certain iv drugs can cause local injury if intravenous line becomes extravasated and Nurse must monitor this**

Guidelines to help ensure correct administration

- **Read medication order carefully- verify**
- **Verify identity of patient with drug order**
- **Read medication label & verify**
  - **Drug itself**
  - **Amount of drug (per tablet, per volume**
  - **Verify suitability for administration by intended route**
- **Verify dosage calculations**
- **Use special handling if drug requires**
- ***DO NOT ADMINISTER ANY DRUG IF YOU DO NOT UNDERSTAND THE REASON FOR ITS USE***

Evaluating and Promoting Therapeutic Effects

- **Is the drug doing the right thing? Evaluation criteria**
  - **Must know rationale for treatment and the nature and time course of desired response**
    - **If do not have this then cannot make judgment of progress**
  - **If desired response do not occur then must act quickly**
    - **Give alternative therapy**
    - **Even if patient gains beneficial responses, must be aware of what drug is supposed to do, because it still might end up badly**
      - **Nifedipine: given for hypertension & angina pectoris: when given to treat hypertension should monitor for reduction in blood pressure; if used for treatment of angina, need to monitor for reduction in chest pain**

Promote Compliance

- **Drugs must be taken correctly**
  - **Wrong dose**
  - **Wrong route**
  - **Wrong time**
- **Educate patients to how to self medicate with specific instructions**
  - **If elderly must also give instructions to another responsible party (elderly might not like this!)**
- **Implement Non-drug measures to enhance drug effects**
  - **Breathing exercises, biofeedback, emotional support, exercise, physical therapy, rest, weight reduction, stop smoking, and sodium restriction (must evaluate individual patient for specific needs)**

Minimize Adverse Effects

- Know patient history
  - Understand disease and treatment and what drug is supposed to do (again, do not give drug blindly!!!)
  - Identify high risk patient
  - Educate patient
  - Know adverse effects of drug and educate patient to these
- Know drug interactions with other medications
  - This is important part of patient history

PRN Decisions

- PRN order (*pro re nata* = as needed or as occasion arises) --
  - nurse has discretion regarding how much drug to give and when to give it
  - Most common for sleeping aids

Patient Education

- **Drug name and therapeutic category (penicillin & antibiotic)- give generic name and trade name**
- **Dosage size**
- **Dosing schedule (PRN not fixed)-what to do if missed?**
- **Route and technique of administration taught**
- **Expected therapeutic response and when it should develop**
- **Non drug measures to enhance therapeutic responses**
- **Duration of treatment**
- **Method of drug storage**
- **Symptoms of major adverse effects, and measures to minimize discomfort and harm**
- **Major adverse drug-drug and drug-food interactions (along with Pharmacist)**
- **Whom to contact in the event of therapeutic failure, severe adverse reactions, or severe adverse interactions**

Chapter 3: Pharmacology and the Nursing Process

- Nursing Process-- 5 steps
  - 1) assessment
  - 2) analysis (nursing diagnosis: you see patient first)
  - 3) planning- individual for each patient
  - 4) implementation- some collaborative with physician and others are independent
  - 5) evaluation- degree to which drug therapy is successful

Preadministration Assessment

- **Establishes the baseline data needed to tailor drug therapy to the individual patient: maximizes benefits and minimizes harmful effects**
  - **Collection of baseline data needed to evaluate therapeutic responses- beneficial**: know the symptoms so you know what baseline data to collect
    - **blood chemistry profiles**
    - **Blood pressure**
    - **Organ enzyme levels (heart, liver, kidney,…)**

  - **Collection of baseline data needed to evaluate adverse effects:**
    - **Even without baseline data, adverse affects may be obvious (hair loss, pain, vomiting, insomnia,…)**
    - **Less obvious are organ functions (i.e., liver, kidney, …)**
  - **Identification of high risk patients:**
    - **Depends on symptoms and drug chosen (if patient has kidney dysfunction and drug is eliminated primarily through kidney, then drug will accumulate and may be toxic)**
      - **Impaired kidney & liver**

- **Allergy to penicillin- ***PRECAUTION*** not to use drug again, and if used must maintain tighter control over patient (watch…)**

- **Assessment of patient's capacity for self-care-**
  - **Must be willing and able to administer drugs in correct dosage and at correct time**
    - **Evaluate patient intelligence**
    - **Patient physical capacity to self administer**
    - **Mental illness (will they take drug?)**
    - **Financial ability to pay for and get drug**
    - **Religious beliefs concerning drugs and medications**
    - **Understanding of patient that drug is needed in prescribed amount (even when they feel better)**
  - **Assess and discuss with physician**

- **Nursing Diagnoses and Analysis of Drug**:
  - Judge appropriateness of prescribed regime
  - Identify potential health problems that drug might cause
  - Determine patient's capacity for self care
- Nurse can question appropriateness of drug!
  - To do this must know action of drug, and
  - contraindications of drug, and
  - Potential benefits vs adverse reactions to drug, and
  - Patient history, and
  - Potential interactions of drug with other medications

- **Planning:**
  - **Define goals**: goal of drug therapy is to provide maximum benefit with minimal harm. Plan ways to do this
  - **Establish Priorities**: requires knowledge of drug put together with patient's unique history. 1st priority is life threatening conditions and reactions that cause acute discomfort that ends in long-term harm
  - **Identifying interventions**:
    - Drug administration
    - To enhance drug effectiveness
    - To minimize adverse effects and interactions
    - Patient education
  - **Establish criteria for evaluation**: is drug working?

- Implementation of care plan
  - Drug administration
  - Patient education
  - Interventions to promote therapeutic effects
  - Interventions to minimize adverse effects
- Evaluation
  - Therapeutic responses
  - Adverse drug reactions and interactions
  - Compliance to regimen
  - Satisfactions with treatment
  - How frequent do you evaluate??
    - Depends on ….. ???
    - Evaluation by lab tests- baseline data vs current data

Chapter 4: Drug Regulation Legislation, Development, Names and Information

- Drug Legislation
  - 1st Law to regulate drugs passed in 1906
    - Stated that drugs should be free of "adulterants"
  - Food, Drug and Cosmetic Act, passed in 1938
    - Regulated drug safety (due to death of >100 people who used new drug- sulfanilamide + solubilizing agent (diethylene glycol) [this caused deaths-antifreeze]
    - All drugs must be tested for safety and must be OK'ed by FDA for marketing

- **Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act**
  - **Passed in 1962 after thalidomide (sedative) cause birth defects in Europe in pregnant women (>10,000 infants born with Phocomelia [gross deformities or absence of arms and legs)**
    - **FDA withheld drug in US so most tragic results not in US**
  - **Required that "proof" of effectiveness and safety before marketing**
- **1970 passed the "*Controlled Substances Act*": specifically for drugs in which there could be potential for abuse**
  - **Schedule I drugs: no accepted medical use in US (heroine, LSD,…)**
  - **Schedule II-V drugs: have accepted medical use but are susceptible to abuse. Potential for abuse becomes LESS as you go from level II to level V**
- **1992: FDA approved "fast track" drugs for AIDS & Cancer**

- **1997: Food and Drug Administration Modernization Act-- 5 provisions of interest for health professionals:**
  - **Fast track system created for AIDS and cancer drugs now includes drugs for other serious, life threatening illnesses**
  - **If a manufacturer plans to stop production of a drug they must inform patients 6 months in advance**
  - **FDA can now require companies to test drugs in children (dosage, ½ life, clearance, effects [receptors different in children than adults])**
  - **Clinical trial data base will be established so that informed decisions can be made about trial drugs**
  - **Drug companies can now give journal articles about "off-label" use of drug [use that has not been evaluated by FDA]. Prior to this manufacturer could not provide evidence for use concerning other illnesses, even though physician could prescribe drug for other illnesses.**

- Table 4-1 Steps in New Drug Development

- Development of new drug is expensive and lengthy
  - 6-12 years
  - Of 5000 compounds that enter testing only one is approved as a new product
- Testing requires 2 principle steps
  - Pre-clinical testing- required before new drug can be tested in humans. 1-5 years of testing in animal models after which drug is awarded "Investigational New Drug" status and clinical trials begin
    - **Test for toxicities**
    - **Pharmacokinetic properties**
    - **Test for potentially useful biologic effects**

  - Clinical testing:
    - **4 phases – may take 2-10 years for completion**
    - **1-3rd phases done before drug is marketed, 4th phase done after marketing**
      - **PHASE I Trials- conducted in normal volunteers. If drug is likely to have severe side effects then trial is conducted in individuals who have the disease (cancer, ….) INFORMED CONSENT**
      - **PHASES II and III- drugs tested in patients to determine therapeutic effects, dosage, range and safety. 500-5000 included in these studies, and for those not taking placebo drug is not taken for more than 3-6 months.**
      - **PHASE IV- new drug released for general use, but population is monitored for effects and adverse reactions (voluntary reporting by prescribing physicians is necessary!!)**
    - **New drugs might have adverse effects not found in clinical trials**
    - **Children, women and geriatric patients not studied much**

- **Limited information on Women**
  - **Women of child bearing age excluded from most Phase I & II studies (fetal safety?)**
  - **Do not know whether women will respond to drugs equally to men (better, worse, differently??)**
  - **Timing of drug with menstrual cycle?**
    - **Hormone fluctuations and cycling**
  - **Not known if following will be same in women**
    - **Drug absorption**
    - **Drug distribution**
    - **Drug clearance**
    - **Drug metabolism**
    - **Drug safety during pregnancy**
- **Limitation on information in children & Aged**

- **Not all adverse effects will be detected prior to release of new drug**
  - **Small number of patients given drug during trials**
  - **Patients carefully selected and do not represent normal population distribution and variety**
  - **Subjects take drug for relatively short time in trials**
  - **Sometimes use only very ill to study in trials**

4-2 New Drugs that were Withdrawn for Safety Reasons

Drug Names

- 3 types of drug names
  - **Chemical name**: chemical make-up of compound: usually too complex for people to remember
  - **Generic name**: assigned by the "United States Adopted Names Council". Ony one generic name/compound (***nonproprietary*** name)
  - **Trade name**: proprietary (brand) name. Name by which drug is marketed
    - Acetaminophen (generic name) has 31 trade names (different formulations of proprietary compound)
    - Trade names must be approved by FDA
    - Trade names **CANNOT** imply unlikely results/success (i.e., "fat-be-gone"….)

- Generic name for a drug is longer and more complex than the trade name
- A single drug can have multiple Trade Names
  - Acetaminophen has >30 Trade Names
  - Recalling Generic name may be easier than trying to remember all the different Trade Names of a drug
  - **More accurate communication** if use Generic name
  - Less confusing for patient to see only one Generic name on label rather than different Trade Names (double dosing?)
  - Trade Names may be similar but contain different drugs (i.e., Monistat 1 and Monistat 3)– confusing!!
    - Excedrin Tablets- contains 3 different drugs (aspirin, acetaminophen and caffeine)– how do you know??

- **Trade Names are too misleading for consumer as well as health care practitioner**
  - We use Trade Names because Pharmaceutical Firms want them! (Politics)
- **Do differences exist between different brands of the same drug? & if so, do they justify the use of Trade Names?**
  - Other companies can market drug once patent has expired from original (~17 years?)
    - All products, generic or brand name, contain the same amount of the same drug
    - Differences in rate and extent of absorption only concern (assumed that **"all FDA approved generic products are therapeutically equivalent to their brand-name counterparts"**

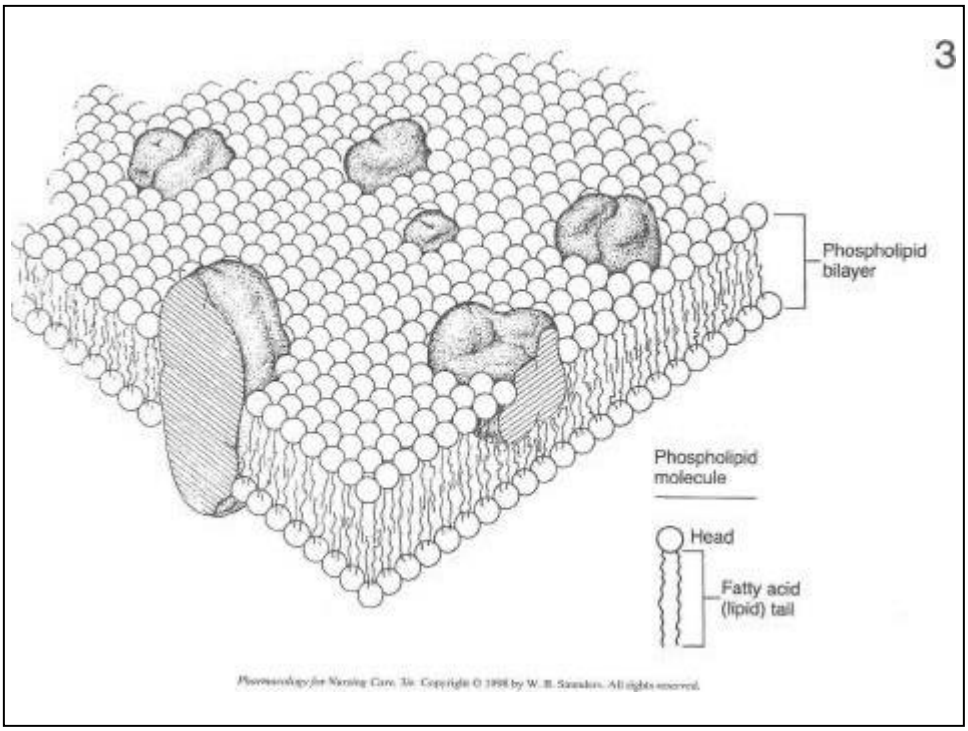
- Try to discourage the use of Trade Names and promote the use of Generic Names for patients!!
- **<u>Over-The-Counter Drugs (OTC)</u>**
    - **Drugs that can be purchased without prescription**
    - **OTC account for >60% of all doses administered**
    - **40% of Americans take at least one OTC drug every 2 days**
    - **The average American medicine cabinet contains 24 OTC preparations**
  - Some drugs that were sold as prescription only are now sold as OTC
    - **Do consumers have the ability & knowledge to self prescribe?**
  - In 1999 the FDA passed a regulation that requires OTC drugs to have informative and easy to understand labels
  - Know sources of drug information to pass on to patients

Chapter 5: Pharmacokinetics

- **Pharmacokinetics**= (drug/poison)+(motion)
  - Study of drug movement throughout the body
  - Drug metabolism
  - Drug excretion
  - **Four pharmacokinetic processes**-
    - Absorption- movement from site of administration into blood
    - Distribution- movement from blood to interstitial space of tissue and then into cells
    - Metabolism- enzymatic alteration of drug structure
    - Excretion- movement of drug and metabolites out of body
  - All of these determine the effective concentration of drug at it site of action

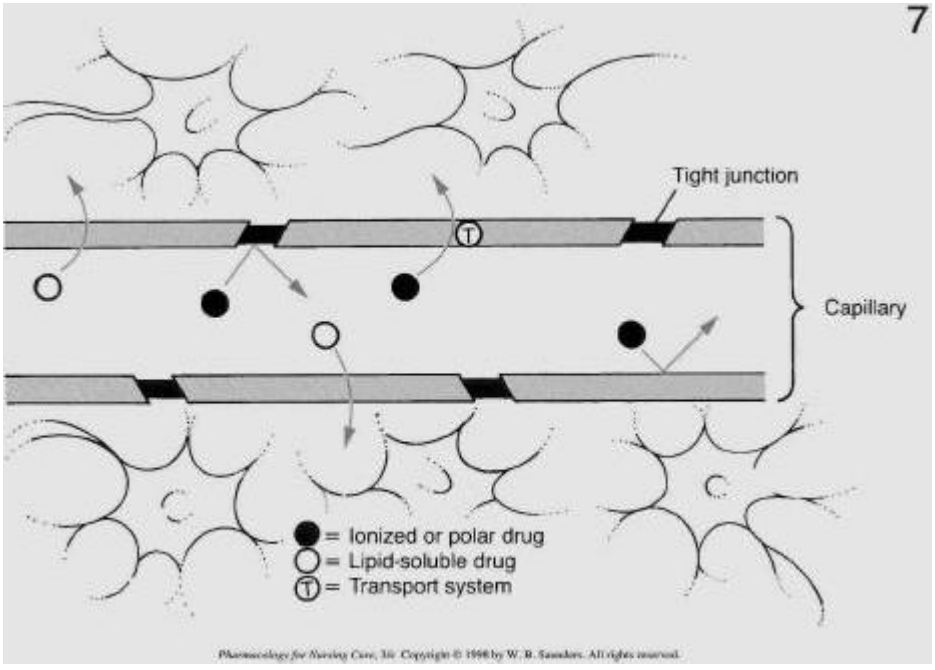
- Application in Therapeutics:
  - Must know action of pharmacokinetics of drug in order to maximize effectiveness of action
    - Must maximize drug at site of action
    - Must minimize side effects of high concentrations of drug (avoid high concentrations) **[Zithromax=Azithromycin]**
      - Scheduling of drug administration
      - Route of administration

- **Membrane Structure**
  - For drugs to move through the body they must move through cell membranes (lipid bilayers)
    - Lipid made up of glycerol (3 carbon backbone) plus long chain fatty acids. Proteins present in lipid bilayer (receptors, …)
    - Glycerol + Fatty acids= lipid -- this can be phosphorylated

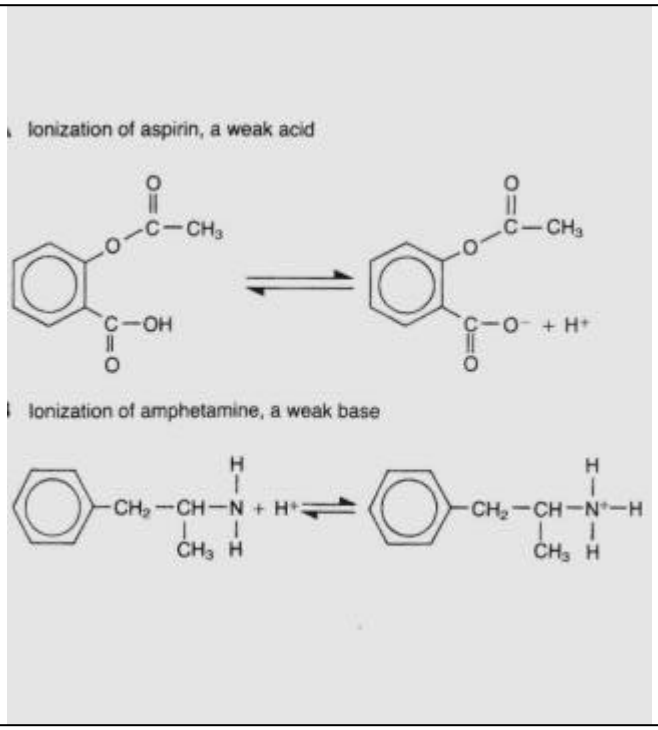


- Phospholipids can be saturated (all bonds full *vs* double bonds between carbon backbone structure of long chain fatty acids) Which is healthier??
- Membrane is polarized
  - Hydrophobic region= long chain fatty acids
  - Hydrophilic region= glycerol backbone + phosphate group
  - Whether a drug is "lipid soluble" depends upon its ability to pass through the charged membrane
- Three ways drug passes across membrane
  - Through channels or pores (carrier proteins)
  - With the aid of a transport system (requires energy)
  - Direct penetration of membrane (most common)
    - Diffusion- movement of molecules from higher to lower concentration
    - Osmosis- movement of water molecules across a semi-permeable membrane from greater water concentration to less

- **Transport systems**
  - Carriers that move drugs from one side of the membrane to the other
    - All carrier systems are selective for molecules they carry
    - Some require energy (ATP) and others do not
  - Most drugs too large to pass through channels or pores
  - Most drugs lack specific carrier molecules
- To directly penetrate membrane drug must be lipid soluble:
  - Polar molecules and ions **CANNOT** cross membrane
    - Charged molecules cannot cross membrane
    - Charge on a molecule may depend upon pH (log of the negative concentration of hydrogen ions) (pH of 1 is very acid)



- **Acid- compound that can give up a hydrogen ion (proton). An acid is a proton DONOR (becomes negatively charged when proton given up)**
- **Base- is a proton acceptor and becomes + charges when it accepts proton**
  - **The process of becoming charged (ion) is called IONIZATION**
    - **Acids tend to become ionized in basic (alkaline) media**
    - **Bases tend to become ionized in acidic media**
      - » **Aspirin is an acidic molecule- in the stomach (acid environment) it remains non-ionized and can pass into the blood; once it moves to the intestine where it is basic, the aspirin becomes ionized and cannot cross the membranes into the blood**
  - **ION TRAPPING** or **pH PARTITIONING**: when there is a pH gradient on either side of the membrane, **acidic drugs will accumulate on the alkaline side**, and **basic drugs will accumulate on the acidic side**
  - **By manipulating urinary pH can use Ion Trapping to draw toxic substances into urine from blood, removing them from the system**



- **Factors affecting drug absorption:**
  - **Drug must dissolve before it is absorbed**
  - **Surface area determines rate of absorption (villi, …)**
  - **Blood flow: where blood flow is high more of the drug is absorbed.**
  - **Lipid soluble drugs absorbed more rapidly**
  - **pH will influence drug absorption**
- **Routes of Administration**
  - **Enteral- gastrointestinal tract absorption (po): oral**
  - **Parenteral- by injection (iv, sc, im)**
    - **Iv has benefits and disadvantages**
      - **No barrier to absorption, rapid onset, use of large fluid volumes, use of irritant drugs (iv lines dilute irritant)**
      - **High cost, inconvenience, difficult to administer, irreversible (slow administration), fluid overload can occur, infection (contaminated needle), embolism (blockage of site distant from administration)- clot, hypotonic death of RBCs, air**

- **Intramuscular**
  - **Only barrier to absorption is capillary wall**
    - **Rate of absorption can be fast or slow determined by**
      - **Solubility of drug**
      - **Blood flow to site of injection**
    - **Poorly soluble drugs can be administered in this manner- can be dissolved as blood flow goes by**
    - **Can be used to have drug absorbed gradually over time (adjuvant therapy– injection in thick bolus)**
  - **Drawbacks to IM injection are**
    - **Discomfort (painful) and inconvenience (not as easy as oral admin)**

- **Subcutaneous**
  - sc similar to im administration
- **Oral**
  - *per os* (by way of mouth)= oral
  - Absorbed from stomach or intestine
  - Must get through epithelial cell barrier and capillary wall
    - **Must pass through cells, not between them**
  - Factors that determine rate of absorption
    - **Solubility and stability (to acid & proteases)**
    - **Gastric and intestinal pH**
    - **Gastric emptying time**
    - **Food in the gut**
    - **Co-administration of other drugs**
    - **Capsule (coating) around drug**

- **Advantages to oral administration**
  - **Easy, convenient, inexpensive (relatively)**
  - **No risk of fluid overload, infection or embolism)**
  - **Can potentially be reversed if overdosed**
    - **Emesis- vomiting**
    - **Catharsis- rapid emptying of small intestine and bowel before absorption (activated charcoal absorbs drugs)**
- **Disadvantages-**
  - **Variability of absorption (young vs old)(empty vs full stomach), pH**
  - **Inactivation by proteases and acid**
  - **Can't be given to comatose patients or non-cooperative patients (will not swallow pills?)**
  - **Inflammation of GI tract and irritation**

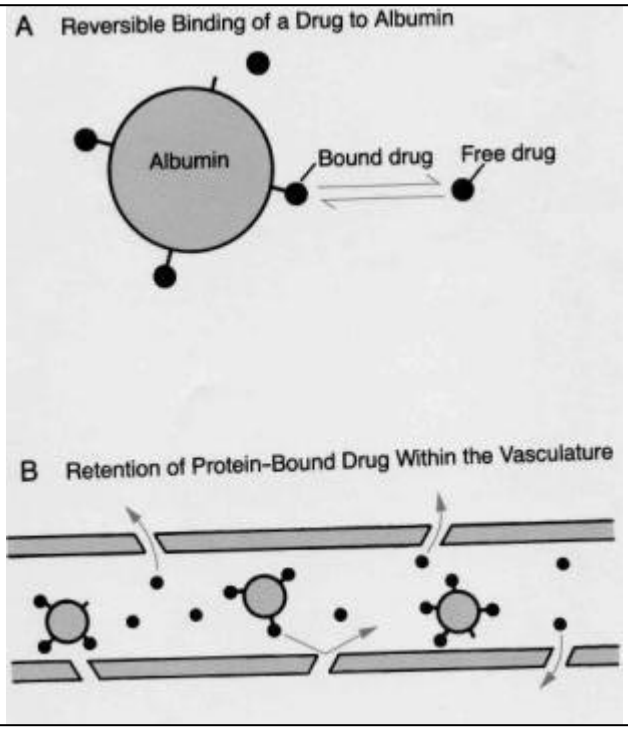
- **Indications for parenteral injections**:
  - Emergencies (quick response to drug required)
  - When plasma drug levels have to be tightly regulated
  - When drugs would be destroyed by pH or enzymes
  - When drugs would not be absorbed through membranes
  - Drugs that might cause severe local injury if administered orally or topically
  - For patients who cannot or will not take oral medication
- **"Packages" for Oral administration**:
  - Tablets
  - Enteric coatings
  - Sustained release preparations

- **Chemical equivalence**- if drug contains the same amount of the identical chemical compound
- **Bioavailability**- if drug is absorbed at the same rate and to the same extent
  - Two formulations of the same drug may be chemically equivalent but differ in bioavialability
- **Tablets**-
  - **Mixture of a drug plus binders and fillers compressed together. If made by different companies can differ in rates of disintegration and dissolution (availability)**
- **Enteric-Coated Preparations**-
  - **Drugs covered with material designed to dissolve in the intestine but not in the stomach (composed of fatty acids, shellac, waxes (protect from acid and pepsin and protect stomach from adverse effects)**

- **Sustained-release-**
  - Capsules filled with tiny spheres that contain drug. Spheres have coatings that dissolve at variable rates. Drug is released at steady rate over number of hours
- **Other ways to deliver drugs-**
  - **Topical-** local therapy: skin, eyes, ….
    - **Transdermal patches- nicotine, ….**
  - **Inhalation-** asthma, oxygen, ….
  - **Rectal/vaginal suppositories-** local and systemic effects
  - **Direct injection into specific tissue/organ-** CNS, heart

- **Distribution**
  - **Blood flow to tissues**:
    - **Rate of delivery to tissues is determines by amount of blood flow to tissue. Most tissues well vascularized**
      - **Low blood flow to abscesses and the centers of solid tumors protect these from effects of drugs**
    - **Drug must leave blood and move into tissue where effect is desired. Most drugs pass between capillary cells, not through them**
  - **Blood-Brain Barrier**:
    - **Unique anatomy of capillaries in CNS. Cells have "tight junctions" in CNS and prevent movement of drug out into cerebrospinal fluid. Only lipid soluble drugs will get across blood-brain barrier.**
    - **Not well developed at birth and neonates more vulnerable to drug treatment than adults (good and bad!)**

- **Placental Drug Transfer**:
  - **No direct blood exchange between mother and fetus**
  - **Drug must cross membranes to get to fetus**
    - **Nonionized compounds pass placenta, ionized compounds excluded**
  - **Some drugs cause**
    - **Birth defects: low weight, mental retardation, gross anatomical defects (thalidomide)**
    - **Drug dependent babies**
    - **Respiratory depressants during delivery retard breathing in neonate**
  - **Protein binding**
    - **Plasma albumin- too large to leave blood, and if drug binds to this it cannot get to target site**
      - **Warfarin (anticoagulant- binds to albumin) & neutalized**
      - **Penicillin- binds to albumin and creates allergic reaction**
      - **Competition between drugs for binding, and displacement of one drug by another may cause level of one drug to rise and cause toxic response**

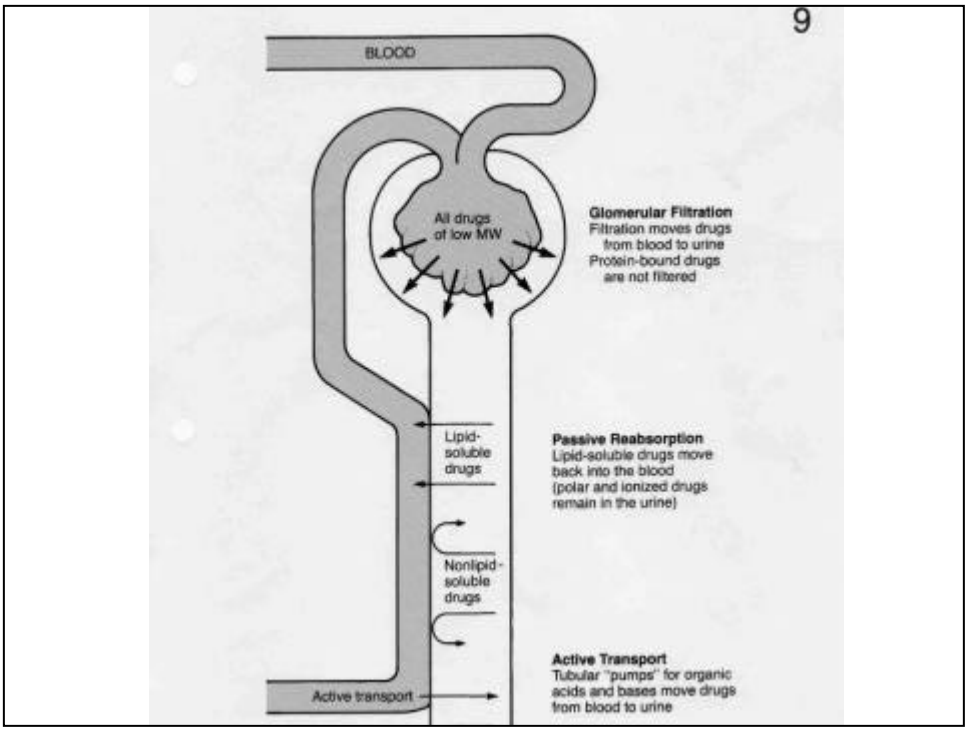

A Reversible Binding of a Drug to Albumin
Albumin
Bound drug
Free drug
B Retention of Protein-Bound Drug Within the Vasculature

- **Entering Cells**
  - **Drug must enter cells to get to target and to undergo metabolism and excretion (if bind to receptors on surface do not need to get in to act on target)**
- **Metabolism**– enzymatic alteration of drug structure
  - **Hepatic drug metabolizing enzymes**
    - **Microsomal enzyme system (cytochrome P450)**
      - **Group of 12 related enzymes**
        - » **CYP1, CYP2 and CYP3 metabolize drugs: these 3 families are composed of other enzymes within the group (i.e., CYP1A,….)**
        - » **Other 9 metabolize steroids, fatty acids, ….**
        - » **Remove alcohols, toxins, … before entering blood stream**
    - **Drug metabolism has 5 consequences:**
      - » **Accelerated renal excretion of drugs**
      - » **Drug inactivation**
      - » **Increased therapeutic action (codeine-→ morphine)**
      - » **Activation of pro-drugs**

- **Special considerations in drug metabolism**
  - **AGE**
    - **Infants do not have full liver function until ~1 year. These children very sensitive to drug therapy and may have toxic effects or unwanted effects**
    - **Older people (>60 years) do not have full liver function**
      - **Related to age**
      - **Related to alcohol**
      - **Related to disease (hepatitis)**
  - Neither of these groups studied extensively for reaction to drugs. Must be aware of these differences!! ()(
- First pass effect- rapid hepatic inactivation of certain oral drugs
  - Give first dose parenterally- bypass liver and get therapeutic dose in system (nitroglycerin under tongue)

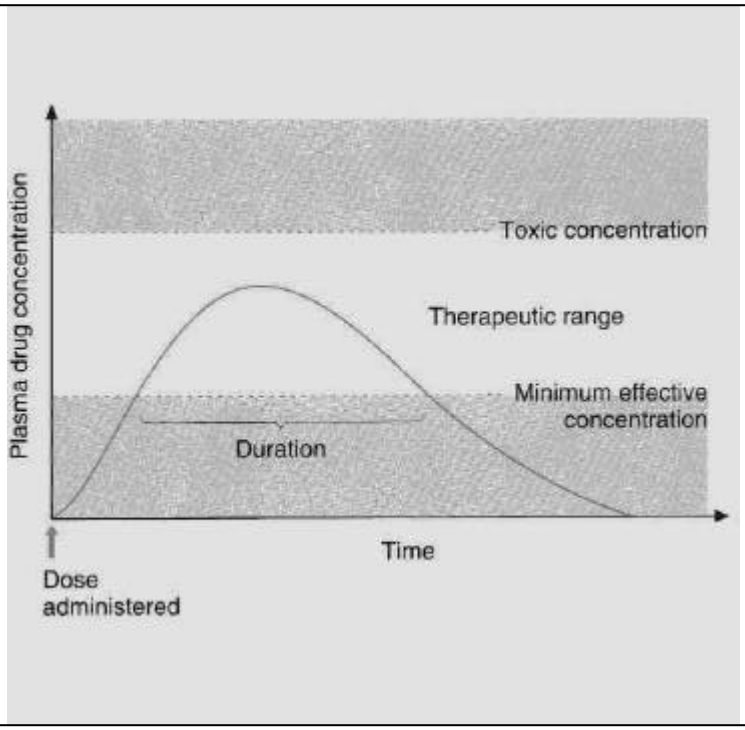
- **Nutritional Status**
  - Hepatic metabolizing enzymes require co-factors (certain trace metals {Zn, Mg, Ca, Mn, Cu, Fe, ….} and vitamins). If not present in diet then hepatic function for clearing drugs is impaired [drug stays longer in system and could become toxic, …)
- **Competition between drugs**
  - When two drugs metabolized by same pathway they compete with each other and decrease the rate at which both agents are cleared and lead to toxic effects in patient

- **Excretion--** Removal of drugs from system
  - Urine, bile, sweat, saliva, breast milk, expired air, kidney
- **Renal Excretion**
  - ***Glomerular filtration***: capillary network & Bowman's capsule. Proteins do not pass across (if drug attached to protein not cleared), but other substances diffuse across and may be actively transported across
  - ***Passive tubular reabsorption***: water and lipid soluble drugs may be reabsorbed back into blood (movement from greater to less concentration)
  - ***Active tubular secretion***: active transport of drugs from blood to urine in tubules

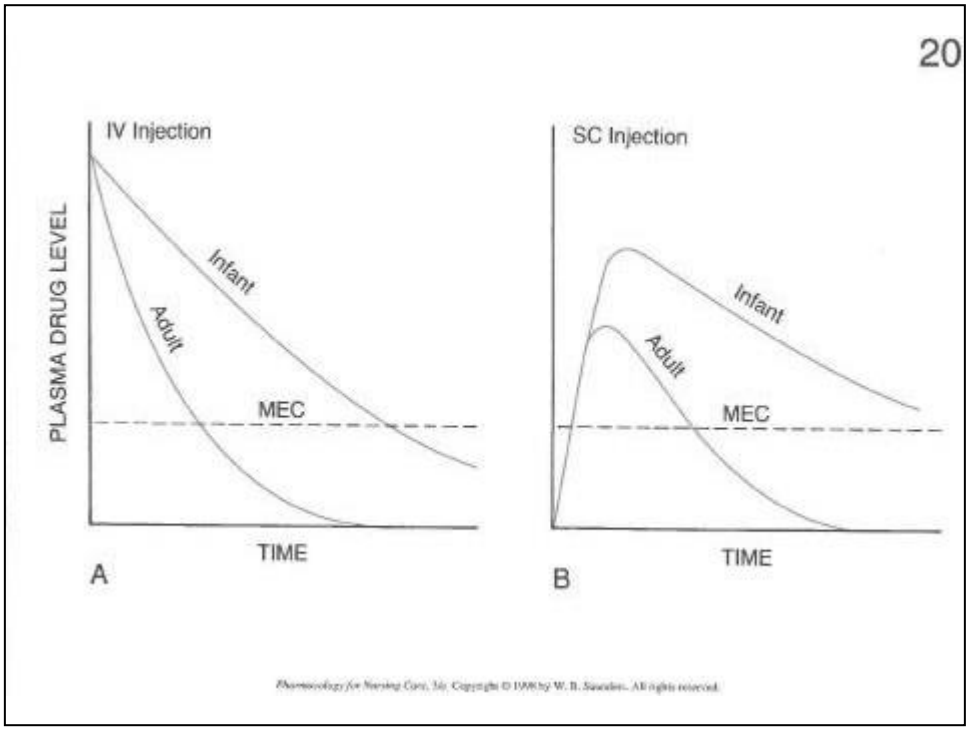

9
BLOOD
All drugs of low MW
Glomerular Filtration
Filtration moves drugs from blood to urine
Protein-bound drugs are not filtered
Lipid-soluble drugs
Passive Reabsorption
Lipid-soluble drugs move back into the blood (polar and ionized drugs remain in the urine)
Nonlipid-soluble drugs
Active Transport
Tubular "pumps" for organic acids and bases move drugs from blood to urine
Active transport

- **Factors that modify renal drug excretion**
  - ***pH-dependent ionization***: converts lipid soluble compounds to ions so they cannot pass across epithelial cells of tubule and stay in urine
  - ***Competition for active tubular transport***: if same transport mechanism is the same for two drugs, competition for receptor will delay clearance of both (can be used to prolong life of drug in body (i.e., penicillin cleared quickly, but if add probenecid at same time removal of penicillin delayed)
  - ***Age***: kidneys of newborns not fully developed, and kidneys of aged not fully functional. Must take into account when dosing patients (text book does not mention aged patient)

- **Time Course of Drug Responses**
  - ***Must regulate***
    - Time at which drug responses start
    - Time they are most intense
    - Time they cease
      - » The four pharmacokinetic processes– absorption, distribution, metabolism, and excretion– determine how much drug will be at it sites of action at any given time
  - ***Plasma levels of drug***
    - Can be measured and adjusted up or down by **changing dosage**, the **timing of administration**, or both
    - Concentration at site of action most important, not plasma level, but it is not possible to measure drug levels at site of action. There is a DIRECT correlation between plasma levels and levels at site of action



- **Minimum Effective Concentration**
  - MEC is the plasma drug level below which therapeutic effects will not occur (drug must be present at or above MEC to be effective)
- **Toxic Concentration**
  - Occurs when plasma level of drug gets too high
- **Therapeutic Range**
  - Range of drug concentrations falling between MEC and toxic concentration that is the therapeutic range. Must maintain concentration of drug within therapeutic range to be most effective. Width of therapeutic range important (the larger, the easier to maintain between)



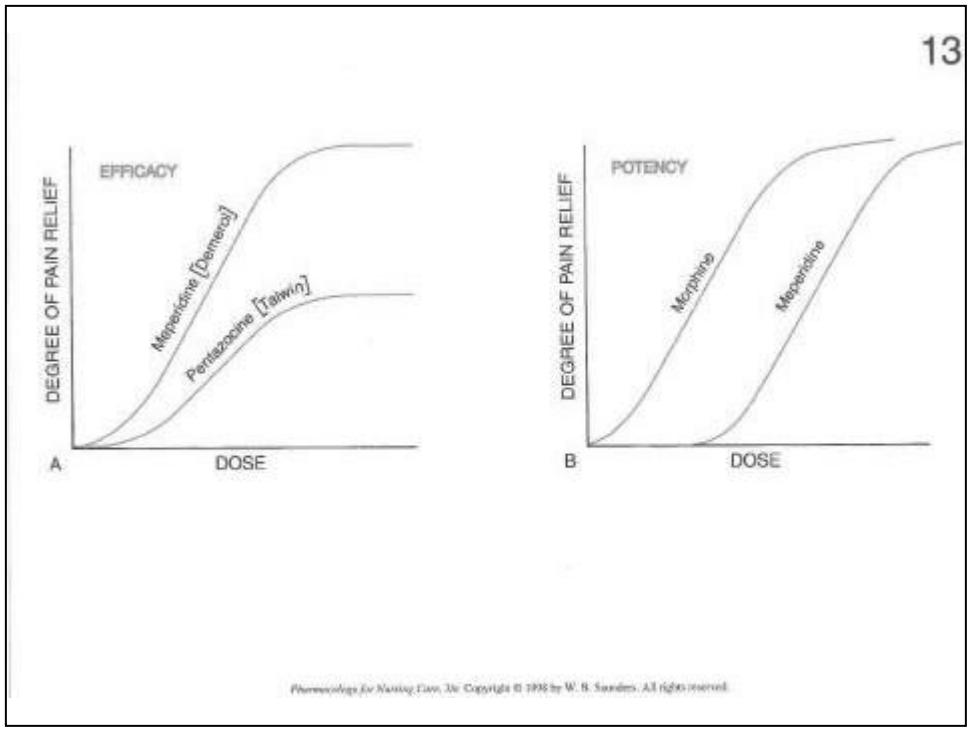
- **Single Dose Time Course**
  - **Rise of drug levels reflect an increase in absorption**
  - **Decline of drug levels reflects processes of metabolism and excretion**
    - **Rate of absorption determines how fast the onset of effects will occur**
    - **Duration of effects is dependent upon the combination of metabolism and excretion as long as drug is above MEC**
- **Drug ½ Life**
  - **Time required for the amount of drug in the body to decrease by 50%. Drugs have short or long ½ lives (minutes to weeks).**
    - **Prior to changing drugs, must be certain that first drug is completely eliminated from body**
  - **The larger the amount of drug in the body the greater the amount lost at each ½ life**
  - **½ life of drug determines dosing interval**

- When single dose of drug given level of drug in plasma simply goes up and then comes down
  - **Multiple doses maintain a steady level of drug in system at a *plateau* (steady level): the amount of drug given is equal to the amount of drug eliminated**
  - **When a drug is administered repeatedly in the same dose, plateau will be reached in approximately four ½ lives**
  - **The degree of fluctuation that can be tolerated, from one dose to another, depends upon the drug's therapeutic range**
    - **Can limit fluctuations by continuous infusion**
    - **By reducing both the dosage size and dosing interval (keeping total daily dose constant)**
  - **When a drug is stopped being administered, it will take approximately four ½ lives to eliminate it from the body (~94% will be eliminated)**

Chapter 6: Pharmacodynamics

- Study of the biochemical and physiologic effects of drugs.
  - Also includes the molecular mechanisms involved in mediating effects of drugs within cell
- ***DOSE-RESPONSE RELATIONSHIPS***:
  - Relationship between the size of the dose given and the response produced
    - Determines the minimum amount of drug that can be used
    - Determines the maximal response that drug can elicit
    - Determines how much you need to increase dosage to produce the desired response

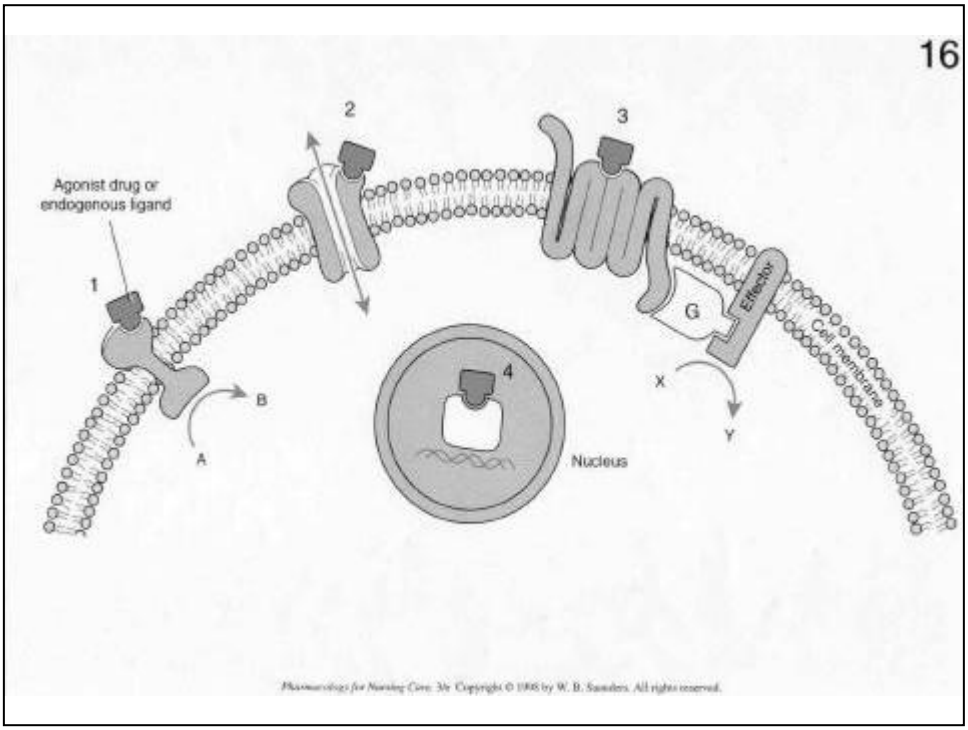
- See figure 6-1for basic features of dose-response
  - Dose response is "***graded***" (versus all-or-none)
    - As dosage is increased the response becomes larger
    - Can tailor drug dose for each individual
    - All-or-none response produces only one intensity of response and cannot be tailored to fit individual (may be too strong or weak for individual)
  - **Phase 1**: occurs at low doses
    - Curve is flat because response is too low to measure
  - **Phase 2**: increase in doses elicits increase in response
    - As dose continues to increase a maximum is reached where further increase in dose will have no effect
  - **Phase 3**: occurs at high dose
    - Higher dose does not increase response
    - Higher dose may elicit toxicity



- ***Maximal efficacy-***
  - Largest effect that a drug can produce. Indicated by height of curve
    - **One drug may have a greater maximal efficacy than another,no matter how much of the second is given**
    - **A drug with high maximal efficacy is not always more desirable than a drug with lower efficacy**
      - **Want to match intensity of response to patient's needs and is hard to do with a drug that produces a very intense response**
- ***Relative Potency-***
  - Refers to the amount of drug we must give to elicit an effect
    - **A drug that produces greater effect at lower dose is more potent, and therefore can be given in smaller doses**
    - **Important only when potency is so low that huge does are required for needed effect (rarely is a concern)**

- **Potency** of a drug has nothing to do with its maximal efficacy
  - Independent of each other
  - Drugs A and B can be equally effective even though one is more potent
  - Drug A can be more effective than drug B even though drug B is more potent

- ***Receptors***
  - Any functional molecule in a cell to which a drug binds to produce its effects
    - May be found on membrane, within membrane, on inner surface of membrane, in cytoplasm, in nucleus
    - Binding to receptor is reversible and competitive



- **Binding to receptor**
  - Drug can ***mimic*** normal hormone (and increase response)
  - Drug can bind to receptor and block normal hormone binding and thereby ***block*** action of normal binding
    - **Receptors are normal control molecules of cell**
    - **Receptor function is regulated by molecules supplied by the body**
    - **Drugs can ONLY mimic or block the action of the body's own regulatory molecules**
    - **Drugs CANNOT give new functions to the cell. Drugs cannot make body (cell) do anything it is not capable of doing**
    - **Drugs help body use pre-existing capacities to the best advantage**
    - **Can theoretically can be made that can alter the rate of any biological process for which receptors exist.**

- In designing drugs it is highly desirable for drug to be selective, and you can use the specificity of receptors to make drugs that are highly specific
  - **Receptor binding will elicit specific cell response**
    - **Second messenger**
      - **cAMP: activates cAMP-dependent protein kinase**
      - **Ca^{++}: activation of calcium binding proteins**
      - **Kinase enzymes: Phosphoylation of specific substrates**
        - » **PKA, PKC, TK, Calcium/calmodulin kinase, MAAPS kinase, ….**
    - **While being selective for receptors, a drug can elicit multiple effects (non-selective)**
      - **Single receptor may control a variety of cell functions**
    - **Specificity does not guarantee safety (botulism toxin highly selective but very toxic)**

- ***Drug-Receptor Interactions***
  - Simple occupancy theory:
    - **Intensity of response to a drug is proportional to the number of receptors occupied by that drug**
    - **Maximal response occurs when all available receptors have been occupied**
    - **This theory is not able to explain why one drug is more potent than another if they bind to the same receptor and both bind maximally to all receptors???**
  - Modified Occupancy Theory
    - **Affinity binding- strength of the attraction between drug and receptor. The > affinity the > potency:::: Drugs with low affinity require higher concentrations to bind to receptor**
    - **Intrinsic activity- ability of a drug to activate its receptor. High intrinsic activity relates to high maximal efficacy (2 drugs can bind to same # of receptors with different intensities of response)**

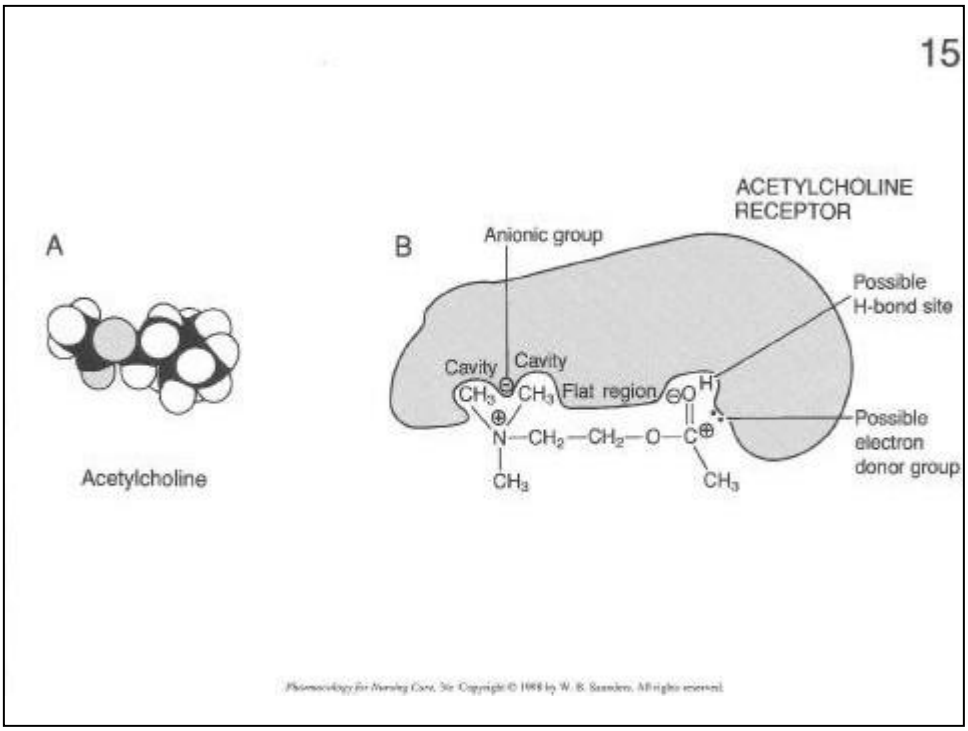
- **Agonists– Antagonists– Partial Agonists**
  - **Agonist**: molecules that activate receptors (mimicry)
    - Has high affinity and high intrinsic activity (binds and activates receptor)
      - Dobutamine- mimics action of NE (norepinephrin) and binds to receptors on heart to increase heart rate
      - Drugs that mimic acetylcholine will acts as agonists to slow heart rate
  - **Antagonists**: produce effects by preventing receptor activation by endogenous regulatory molecules and drugs
    - Has high affinity for receptor but no intrinsic activity (binds to receptor but does not activate receptor)
    - Effect depends upon how much agonist is present- act by competition, and the greater the agonist concentration the greater the antagonist concentration must be to effectively block (competitive vs non-competitive antagonists)
    - Antihistamines act as antagonists

- **Partial Agonists**
  - **Has moderate intrinsic activity & therefore the maximal effect tat a partial agonist can produce is lower than that of a full agonist**
    - **Can act as antagonists as well as agonists**
      - **May be able to block the effects of an agonist by binding to the same receptors. Does not have same level of intrinsic activity and therefore is not as "active", but is able to block binding of more active drug.**

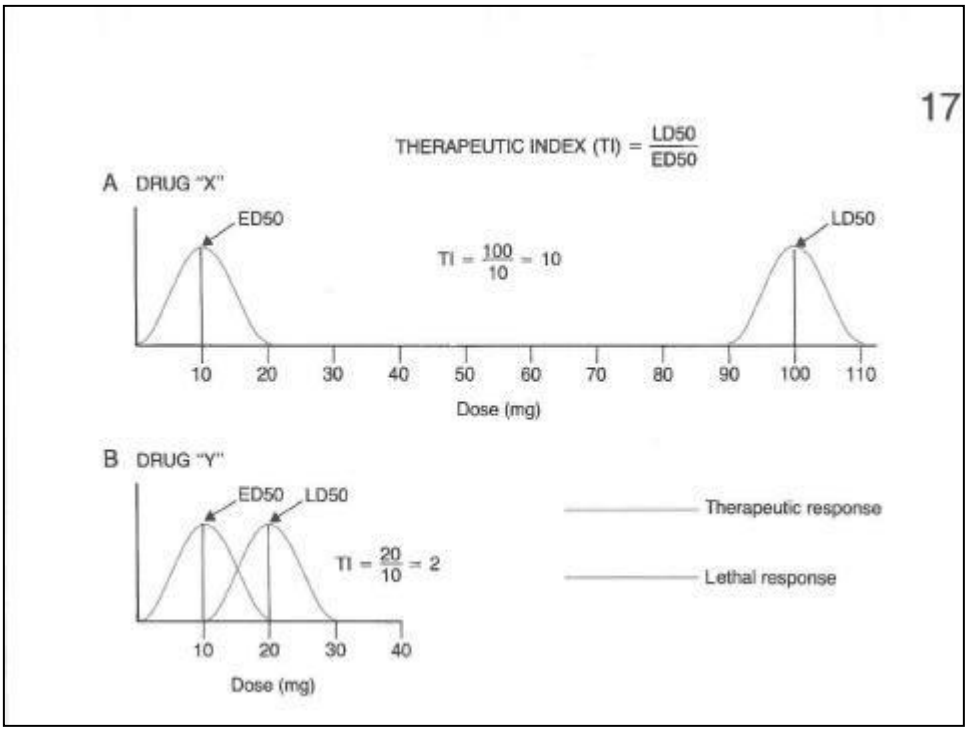
- **Receptor Families**
  - **Cell membrane embedded enzymes-**
    - **span full width of membrane**
    - **Ligand binding domain is external and catalytic binding region is on inside of membrane**
  - **Ligand-gated ion channels**
    - **Span membrane**
    - **Regulate flow of ions in and out of cells (specific for certain ions)**
    - **When ligand binds channel opens allowing ions to flow either inward or outward (determined by ion concentration on either side of membrane)**

- **G protein coupled receptor systems**
- **Receptor**
  - **G protein– binds GTP to activate action. In order to turn off the GTP must be hydrolyzed to GDP. Mutations in some receptors are such that they lose GTPase activity and are turned on all the time (can lead to unregulated cells growth)**
  - **Effector-- ion channel or enzyme**
- **Transcription Factors**
  - **Found with the cell rather than on the surface (on DNA in nucleus)**
  - **Responses are delayed (hours to days)**
  - **Regulate protein synthesis through RNA synthesis**
  - **Receptors to Steroids found in cytoplasm**
    - **Testosterone/ Estrogen/ Progesterone/ Cortisol**
- **Receptors have constant turnover**
    - **Receptor up-regulation- use of antagonists may cause increase in receptor number and result in hyperactivity when drug withdrawn**
    - **Receptor down-regulation- desensitized/refractory**

- **Some drug interactions do not involve binding to receptors**
  - Act directly on chemical (i.e., antacid, antiseptics, alcohol, laxatives & chelating agents (these bind to ions like $Ca^{++,}$ Hg^{++} and inactivate or remove ion)
- **Patient Variation to drug effects & dosage**
  - Variability of receptor numbers on target cells
  - ½ life in each patient
  - Ability to follow requirements for administration of drug
  - ED_{50} -- (effective dose)
    - Dose at the middle of the frequency distribution curve
    - Dose that is required to produce a defined therapeutic response in 50% of the population (dose selected for initial treatment & then can adjust up or down)



- **Therapeutic Index**
  - **A measure of a drug's safety**
  - **Defined as the ratio of a drugs LD_{50} to its ED_{50}**
    - **LD50 is the dose that is lethal to 50% of the animals treated**
  - **A *small therapeutic index* indicates that a drug is UNSAFE while a *large therapeutic index* indicates that the drug is relatively SAFE.**
    - **LD_{50}/ED_{50} ratio:: if lethal dose is 100mg and the effective dose is 10mg there is a 10X difference and indicates that it should be safe to take the medication at the 10mg level.**
    - **If a drug is to be deemed SAFE, the highest dose required to produce therapeutic effects must be substantially LOWER than the lowest dose capable of causing death**



Chapter 7: Drug-Drug and Drug-Food Interactions

- Occurs whenever a patient take more than one medication
  - **Includes OTC drugs as well as prescription**
    - ***Heard on TV Psychiatrist discussing effects of Ginseng migraines and he did mention that little is known about drug interactions, long-term effects, and effects on such things as pregnancy!***
  - ***Intensification of effects one or both drugs***
  - ***Reduction of effects of one or both drugs***
  - ***Production of a new response that neither drug elicits by itself***

- **Intensification of effects**
  - Potentiative: one dug may intensify the effect of another
    - **Synergism**- two drugs act to increase the effect of each other to a level greater than the additive effect of either one alone (may be harmful or beneficial)
    - **Cooperative**- one drug enhances the effect of another drug without any effect on its own actions
      - Can be detrimental or beneficial
        - » If one drug prevents the breakdown of another by inhibition of enzymes, then there in a potentiative effect
        - » If two drugs elicit similar effects to each other the end result may be harmful (two anti-clotting drugs taken together)
- **Reduction of effects**
  - Inhibitory effects resulting in:
    - Reduced therapeutic effect
    - Reduced adverse effects

- **Mechanisms of Drug-to-Drug Interactions**
  - **Direct Chemical or Physical**
    - **Most occur when drugs are in solution in IV**
      - **Can form a precipitate (if precipitate seen solution should be discarded!!)**
      - **Not all interactions of drugs leave a precipitate:: NEVER COMBINE TWO OR MORE DURGS IN THE SAME IV CONTAINER, unless it has been proven that there is no adverse reaction**
  - **Pharmacokinetic Interactions**
    - **Altered absorption- drug interactions affect absorption (enhancement or inhibition)**
      - **Elevation of gastric pH by antacids prevent proper absorption of drugs from stomach (raises pH)**
      - **Laxatives reduce absorption by accelerating passage through intestine**
      - **Induction of vomiting decreases ability to absorb**
      - **Drugs that reduce regional blood flow decrease absorption**

- **Altered Distribution**
  - **Competition for protein binding**
    - **Binding to plasma albumin**
    - **Alteration of plasma pH (extracellular pH)**
- **Altered Metabolism**
  - **Some drugs decrease and others increase metabolism**
    - **Catabolism by P450 (CYP family of liver enzymes used to detoxify drugs, poisons, alcohols, PAHs, etc….) TABLE 7.1 summarizes CYP enzymes that detoxify specific drugs**
- **Altered Renal Excretion**
  - **Alteration of filtration, reabsorption and secretion)**
- **Interactions at the same receptor**
  - **Competitive vs Non-competitive (same receptor site vs different site on receptor to alter shape)**

  - Interactions resulting from drugs with similar actions acting at separate sites
    - **Can act at different receptors that induce different signal transduction pathways (PKC vs cAMP vs TK) that have an end result of the same action, will inhibit one pathway**
- **Clinical Significance of Drug-Drug Interactions**
  - Risk of serious drug interactions directly proportional to the number of drugs individual is taking
    - **6-10 drugs common to take at one time**
    - **Drugs with a low therapeutic index**
      - **Drugs that produce a modest increase in drug levels can result in toxicity (STUDENTS EXPLAIN)**
    - **Minimize potential dangerous interactions by:**
      - **Reducing # of drugs taken**
      - **Take thorough drug history: find out all drugs and unusual reactions that patient has had and is taking (patients taking illicit drugs??? Or OTC???)**
      - **Monitor early signs of toxicity**

- **DRUG-FOOD Interactions-** **depends on food and drug**
  - Decreased absorption
    - **Food decreases rate and extent of drug absorption**
      - **Calcium containing foods and tetracyclin (bind to calcium and complex cannot be absorbed)**
      - **High fiber foods reduce absorption (like digoxin for heart)**
    - **Increased absorption**
      - **High calorie food more than doubles the absorption of squinavir (drug for HIV infection). If drug taken without food absorption is insufficient for antiviral activity**
    - **Grapefruit juice may inhibit metabolism of certain drugs and lead to toxicity levels (inhibits cytochrome P450 enzymes**
  - **MAO inhibitors (monoamine oxidase- anti-depressants)**
    - **React with foods containing tryamine (aged cheeses, yeast extracts, Chianti wine, sausage, pepperoni, etc…) & increase blood pressure to dangerous levels**

- **Timing of Drug administration and Meals**
  - If food affects absorption then must decide on whether drug will cause upset stomach if taken without food or have decreased absorption if taken with food
    - **Choose alternative drug?**
    - **Increase dose if taken with food?**
    - **Take shortly before or after meal?**

Chapter 8: Adverse Drug Reactions

- Adverse Drug Reaction (ADR)
  - Any noxious, unintended and undesired effect that occurs at normal drug doses
    - **Mild reactions:**
      - **Drowsiness**
      - **Nausea, itching**
      - **Rash**
    - **Severe reactions:**
      - **Respiratory depression** **Neutropenia**
      - **Hepatocellular injury**
      - **Anaphylaxis** **Hemorhage**

- **ADRs most common in**
  - **Elderly (>60 years old)**
  - **Very young (1-4 years)**
  - **Patients taking more than one drug**

- **Side effect: "nearly unavoidable secondary drug effect produced at therapeutic doses**
  - **Intensity is dose dependent**
  - **Occur immediately after initially taking drug OR may not appear until weeks after initiation of drug use**
- **Toxicity: "an adverse drug reaction caused by excessive dosing"**
  - **Coma (xs morphine)** **Neutropenia [lower WBC count] (anti-cancer drugs make patient more susceptible to disease)**

- **Allergic Reactions**
  - **Immune response due to sensitization to drug (anaphylaxis to penicillin)**
    - **Aspirin and sulfonamide drugs cause allergic reactions**
- **Idiosyncratic Effect**
  - **Defined as an "uncommon drug response resulting from a genetic predisposition**
    - **Paralysis due to succinylcholine (drug used to produce skeletal muscle flaccid paralysis). Genetically predisposed individuals do not have enzymes to metabolize succinylcholine and longer effects occur)**
- **Iatrogenic Disease**
  - **"disease produced by physician"/ or by drugs**
    - **Taking certain anti-psychotic drugs may induce a syndrome whose symptoms are identical to Parkinson's Disease. Since this is (1) drug induced and (2) essentially identical to a naturally occurring pathology, it is called iatrogenic disease**

- **Physical Dependence**
  - **Long-term use of drug may lead to dependence (opioids, alcohol, barbituates, amphetamines)**
  - **Body adapts to drug so that if drug discontinued then abstinence syndrome will develop**
- **Carcinogenic Effect**
  - **Certain medications lead to cancer**
    - **May take >20 years to develop after initial exposure**
    - **Tumor promotion versus tumor initiation**
      - » **Initiation can occur years before promotion occurs**
      - » **Diethylstilbestrol (DES)-- hard to study (used to stop spontaneous abortion: lead to vaginal and uterine cancers years later in fetus' that had been exposed to this drug *in utero.***
- **Teratogenic Effect**
  - **Drug induced birth defect**

- Hard to determine whether symptom due to drug
  - Did symptoms appear shortly after the drug was first administered?
  - Did symptoms abate when the drug was discontinued?
  - Did symptoms reappear when the drug was reinstituted?
  - Is the illness itself sufficient to explain the event?
  - Are other drugs in the regimen sufficient to explain the event?
- Adverse Reactions To New Drugs
  - May not have enough and long term studies to determine all potential effects
    - Be alert for unusual responses and symptoms
    - Report symptoms to MEDWATCH on internet (be first to ID!!)

Chapter 9: Individual Variation in Drug Responses

- Body weight and composition
  - Drug achieves a higher concentration in smaller people given the same dosage (will produce a more intense effect)
    - Dosages must be adapted to size
    - The "body surface area" calculation is better than body weight because it takes into account weight as well as how fat or lean the person is (% body fat)

- **Age**
  - Infants very sensitive to drugs: due to organ immaturity and/or receptor numbers on cells
  - Elderly very sensitive to drugs- due to organ system degeneration (decreased metabolic inactivation) and receptor number)
- **Gender**
  - Response is different to same drug and dosage between men and women
    - Some more effective in men, some more effective in women
      - Until recently, all drug research done in males
        - » Alcohol metabolized more slowly in women
    - Hormonal effects??

- Pathophysiology (how disease affects responses to drugs)
  - Kidney-
    - Reduce drug excretion: drugs accumulate in body
    - Must decrease dosage of drug until kidney function back to normal
  - Liver
    - Site of drug de-toxification and metabolism
    - Drug will accumulate to toxic levels in body
- Acid-Base Imbalance
  - Alters absorption, distribution, metabolism, excretion
    - Drug will accumulate on side of membrane where pH most favors ionization of drug (pH partitioning across membrane)
      - Acidic drugs accumulate on alkaline side & basic drugs accumulate on acidic side

- **Breathing in CO_2 will cause extracellular pH to decline (become more acid)**
- **Phenobarbitol (a weak acid) moves from blood plasma into cells when blood pH is acid (moves into cells where pH is higher {alkaline}) and cannot get to target sites**

- Altered Electrolyte Balance
  - Electrolytes (K, Na, Ca, Mg) are important in cell physiology and function (especially muscles and nerves)
  - Electrolytes **DO NOT** seem to be important to responses to drugs?? Rare occurrence.
    - **Digoxin (used to treat heart disease) is affected by levels of K**
      - **When levels of K are low digoxin causes dysrhythmias**

- **Tolerance**
  - **Pharmacodynamic tolerance**
    - **Associated with long-term administration of drugs (such as morphine and heroin)**
    - **Patient requires increased doses to produce effects seen at earlier times**
      - **Increased dose produces increased levels of drug in blood over "pre-tolerance" levels**
    - **MEC is increased (minimum effective concentration) that is due to chronic receptor stimulation and down regulation of receptors**
  - **Metabolic Tolerance**
    - **Tolerance due to accelerated drug metabolism**
    - **Induced by synthesis of increased levels of liver enzymes**
    - **Increase in dosage of drug to maintain level of drug in blood that is equal to "pre-tolerance levels"**

- **Tachyphylaxis**
  - **Form of tolerance defined as a reduction in drug responsiveness brought on by repeated dosing over a short time**
  - **Rare occurrence**
  - **Results from depletion of a co-factor that is needed**
    - **Patch that is worn 24 hours/day gives no time for replacement of co-factor**
    - **If used intermittently, co-factor can be replaced**

- **Placebo Effect**
  - **Preparation that has no therapeutic value**
  - **Any response if due to patient's psychological reaction**
    - **Used in research as a control medication to examine effects of drug on disease (rather than not giving anything)**
  - **These effects are REAL (not just "in the head") and important in therapy**
    - **Not all placebo effects are beneficial (positive attitude of patient)**

- **Genetics** (***idiosyncratic effects***)
  - **Mostly through rate of metabolism of drug**
  - **Some effects due to differences in enzyme levels in organs (RBCs, liver, etc…)**
- **Variability in Absorption**
  - **Differences in manufacturing processes affect rate of absorption of drug**
  - **Previously addressed factors (pH, food, peristalsis, …)**
- **Bioavailability** (*in oral preparations*)
  - **Ability of drug to reach systemic circulation from site of administration**
    - **Different preparations of same drug differ**
      - **Tablet disintegration time**
      - **Enteric coating**
      - **Sustained release formulations**

Chapter 10: Drug therapy during Pregnancy and Breast-Feeding

- 1/3 to ½ of pregnant women take at least one prescription drug and most take more
  - Some used to treat pregnancy side effects
    - Nausea
    - Constipation
    - Pre-eclampsia
  - Some medications used to treat chronic disorders
    - Hypertension
    - Epilepsy
    - Infectious Diseases
    - Diabetes
    - Cancer
  - Drugs of abuse (alcohol, nicotine, cocaine, heroine)

- Must balance risks vs benefits of drugs during PG
  - Affect fetus more than mother?
  - Teratogenic effects
  - Mother's health affects fetus—
    - Chronic asthma is more dangerous to the fetus than the drugs used for treatment (mother's who do not take medication for asthma the incidence of stillbirths is doubled!!)
  - Pregnancy alters drug disposition and excretion processes
    - By 3rd trimester renal blood flow is doubled with an increase in glomerular filtration and elimination of drugs increases (**therefore will need an increased dosage of drug to compensate**)
    - Tone and motility of intestines (peristalsis) decrease in PG (**more time for drugs to be absorbed**)

- ***All* drugs can cross the placenta**
  - **Lipid soluble cross more easily**
  - **Ionized, highly polar or protein bounds cross with difficulty**
    - **Nicotine (smaller babies)**
    - **Alcohol (dependence)**
    - **Cocaine/heroine/morphine (addictive to fetus)t**
    - **Bacterial and viral infections**
  - Teratogenesis
    - **"to produce a monster"-- gross malformations**
      - **Cleft palate**
      - **Clubfoot**
      - **Hydrocephalus**
      - **Spina bifida**
      - **Behavioral and biochemical anomalies**
    - **Major structural abnormalities occur in ~ 6% of fetus' {only 3% of all birth defects due to drugs**

- **Teratogenesis**
  - **Sensitivity of fetus to drug is dependent upon developmental stage and when drug is given in relation to the developmental stage**
  - **3 stages of embryonic development**
    - **Pre-implantation (conception → week 20**
    - **Embryogenic period (week 3 → week 8)**
    - **Fetal period (week 9 → term)**
      - **During pre-implantation and embryonic stages the teratogen acts in an all-or-none response, i.e. , is dose is high enough the fetus will die, if dose is sublethal fetus will recover**
      - **Gross malformations produced by exposure to teratogens during the embryonic period (1st trimester)**
      - **Exposure during the 2nd and 3rd trimesters usually results in organ dysfunction rather than gross malformations**

- **Few drugs considered to be teratogenic: hard to prove**
  - **Incidence of congenital anomalies is low**
  - **Animal test may not be applicable**
  - **Prolonged exposure may be necessary**
  - **Teratogenic effects may be delayed**
  - **Behavioral effects are hard to document**
  - **Controlled experiments cannot be done in humans**
- **To prove a drug is a teratogen**:
  - **Drug must cause a characteristic set of malformations**
  - **It must act only during a specific window of vulnerability (weeks 4 through 7 of gestation)**
  - **Incidence of malformations should increase with increasing dosage and duration of exposure**
- **Risk of malformation with most teratogens is only ~10%**

- 1983 FDA classified drugs into 5 categories according to probable risks to fetus
  - A. Remote risk of fetal harm
  - B. Slightly more risk than A
  - C. Greater risk than B
  - D. Proven risk of fetal harm (risk may be acceptable)
  - X. Proven risk of fetal harm (risk of use outweighs potential benefits)
- Pregnant women should avoid drugs completely
  - If PG woman has been exposed:
    - Find out exactly when drug was taken– if not during weeks 2-8 then patient should be reassured that risk of malformation is minimal & 3% of all babies have some kind of malformation

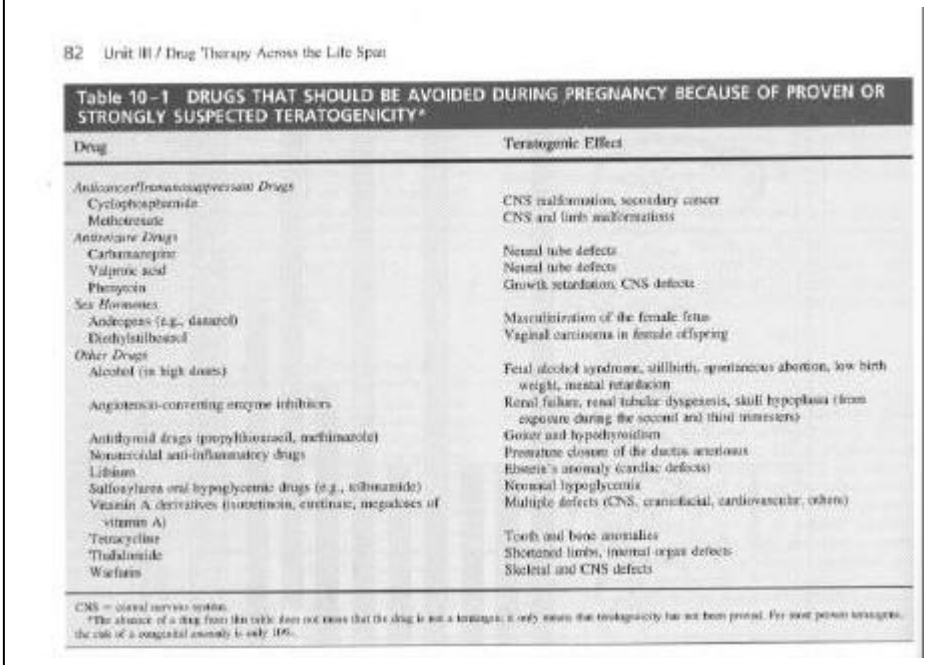


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Table 10–1 DRUGS THAT SHOULD BE AVOIDED DURING PREGNANCY BECAUSE OF PROVEN OR STRONGLY SUSPECTED TERATOGENICITY*

Drug	Teratogenic Effect
Anticancer/Immunosuppressant Drugs	
Cyclophosphamide	CNS malformation, secondary cancer
Methotrexate	CNS and limb malformations
Anticonvulsant Drugs	
Carbamazepine	Neural tube defects
Valproic acid	Neural tube defects
Phenytoin	Growth retardation, CNS defects
Sex Hormones	
Androgens (e.g., danazol)	Masculinization of the female fetus
Diethylstilbestrol	Vaginal carcinoma in female offspring
Other Drugs	
Alcohol (in high doses)	Fetal alcohol syndrome, stillbirth, spontaneous abortion, low birth weight, mental retardation
Angiotensin-converting enzyme inhibitors	Renal failure, renal tubular dysgenesis, skull hypoplasia (from exposure during the second and third trimesters)
Antithyroid drugs (propylthiouracil, methimazole)	Goiter and hypothyroidism
Nonsteroidal anti-inflammatory drugs	Premature closure of the ductus arteriosus
Lithium	Ebstein's anomaly (cardiac defects)
Sulfonylurea oral hypoglycemic drugs (e.g., tolbutamide)	Neonatal hypoglycemia
Vitamin A derivatives (isotretinoin, etretinate; megadoses of vitamin A)	Multiple defects (CNS, craniofacial, cardiovascular, others)
Tetracycline	Tooth and bone anomalies
Thalidomide	Shortened limbs, internal organ defects
Warfarin	Skeletal and CNS defects

CNS = central nervous system.
*The absence of a drug from this table does not mean that the drug is not a teratogen; it only means that teratogenicity has not been proved. For most proven teratogens, the risk of a congenital anomaly is only 10%.

- **Drug Therapy during Breast Feeding**
  - Drugs get through breast milk and can effect infant
  - Little research done on this aspect because of dangers involved in these studies
    - **Concentration of drugs differ in milk**
      - **Lipid soluble drugs are in higher concentration**
    - **Generally most drugs are in too low a concentration to be harmful to infant**
- **Things That Can Minimize Risk**:
  - Dose after breast feeding
  - Take drugs with short ½ life
  - Take drugs that are not found in breast milk
  - Avoid drugs known to be hazardous (Table 10-3)

Chapter 11: Drug Therapy in Pediatric Patients

- Patients who are young or old respond differently to drugs than do middle aged people
  - Greater variation
  - Generally more sensitive (organ immaturity in infants and organ degeneration in older people)
  - Pediatrics- all patients under age 16
    - **Pre-mature infants (< 36 weeks gestation)**
    - **Full-term infants (36-40 weeks gestational age)**
    - **Neonates (1st 4 weeks post-natal)**
    - **Infants (5-32 weeks postnatal)**
    - **Children (1-12 years)**
    - **Adolescents (12-16 years)**

- **Very Young Patients**
  - At risk for prolonged and intense responses
    - Drug remains above MEC level longer in infants than adults
  - **Response of Infants due to differences in**:
    - Drug absorption- absorption of drugs IM is greater in infants than neonates and adults
    - Renal drug excretion (reduced in infants)
    - Hepatic drug metabolism (low in new born)
    - Protein binding of drugs (albumin lower in infants)
    - Exclusion of drugs from CNS by blood-brain barrier (not sully developed in infancy making infant much more susceptible to drugs)
  - ***By one year- pharmacokinetic response similar to adult (except metabolize drugs faster till ~ 2 and falls again at puberty)***
    - **Approximate child's dose= body surface area X adult dose/1.73 m^2**

Table 11–3 ADVERSE DRUG REACTIONS UNIQUE TO PEDIATRIC PATIENTS

Drug	Adverse Effect
Androgens	Premature puberty in males; reduced adult height from premature epiphyseal closure
Aspirin and other salicylates	Severe intoxication from acute overdose (acidosis, hyperthermia respiratory depression); Reye's syndrome in children with chickenpox or influenza
Chloramphenicol	Gray syndrome (neonates and infants)
Glucocorticoids	Growth suppression with prolonged use
Fluoroquinolones	Tendon rupture
Hexachlorophene	CNS toxicity (infants)
Nalidixic acid	Cartilage erosion
Phenothiazines	Sudden infant death syndrome
Sulfonamides	Kernicterus (neonates)
Tetracyclines	Staining of developing teeth

- **If exposure did occur during organogenesis then…**
  - **Find a reference (Briggs et al., "Drugs in Pregnancy and Lactation") to determine the type of malformation expected**
  - **Give at least 2 ultrasound exams to determine extent of injury**
  - **If malformation severe, termination of PG might be considered**
  - **If malformation is minor, then surgery can be planned**

– Drug therapy during breast feeding

- **Drugs can be excreted in breast milk in high enough concentrations to affect the infant**
- **All drugs can be detected in milk, but concentrations usually too low to be of concern (breast feeding is usually safe)**
  - **Take medication immediately after feeding**
  - **Take drugs that have short ½ life**
  - **Take drugs that will not get into milk**
  - **Avoid drugs that are known to be hazardous**

Chapter 12: Drug Therapy in Geriatric Patients

- Elderly constitute 12% of the population but consume 31% of prescribed drugs in US
  - **Elderly more sensitive to drugs and exhibit more variability in response**
    - **Altered pharmacokinetics (organ degeneration)**
    - **Multiple and severe illnesses**
    - **Multiple drug therapy and usage**
    - **Poor compliance**

"Individualization of treatment is essential: each patient must be monitored for desired responses and adverse responses, and the regime must be adjusted accordingly"

- Geriatric patients will vary quite a lot from one patient to another
  - **Physically fit** patients respond differently than out of shape
  - **Absorption- percentage** of absorption DOES NOT usually change with age, but **rate** may be slowed (drug response may be delayed)
    - Gastric acidity may be increased in aged affecting absorption of certain drugs
  - **Distribution-** in aged there is:
    - **Increased body fat**- reduces plasma levels of lipid soluble drugs
    - **Decreased total body water**- increases concentration of water soluble drugs and intensity of response
    - **Reduced concentration of serum albumin**- malnourishment

- **Metabolism**: hepatic functions decrease in elderly and drug levels increase (amount of dysfunction variable)
- **Excretion**: decline of renal function in elderly (variable)- therefore increase drug levels in plasma
  - Determine renal function by *creatinine* clearance rates
- **Pharmacodynamic Changes**: alterations in receptor levels may change on a number of cells, but mostly unknown
  - if receptors decrease then response to drugs will also ????????
  - Decreased affinity of receptors
  - Increase in receptor number and affinity in certain organs???

- **Adverse Drug Reactions (ADRs)**
  - 7 times more common in elderly (due to multiple factors and not just aging)
    - **Drug accumulation secondary to reduced renal function**
    - **Polypharmacy (treatment with multiple drugs)**
    - **Greater severity of illness**
    - **Presence of multiple pathologies**
    - **Increased individual variation**
    - **Inadequate supervision of long-term therapy**
    - **Poor patient compliance**
  - **ADR's can be avoidable**
    - **Take thorough drug history (Rx and OTC)**
    - **Account for changes with age**
    - **Start therapy with low doses**
    - **Monitor drug plasma levels**
    - **Monitor for drug-to-drug interactions**
    - **Dispose of old medications**

- **Promoting Compliance in Geriatric Patient**
  - **>40% of geriatric patients fail to take medications properly**
  - **Results in therapeutic failure or toxicity**
- **Steps to increase compliance**:
  - **Simplify regimen (smallest possible number of drugs)**
  - **Clearly EXPLAIN treatment plan (oral and written)**
  - **Choose appropriate dosage form (liquid vs pill, etc…)**
  - **Label drug containers clearly and choose ones that easily open**
  - **Suggest use of calendar, diary or daily pill counter/ container**
  - **Use of family or friend to ensure compliance**
  - **Monitor for therapeutic responses, ADRs, Plasma drug levels**